Remarks

Based on the currently pending claims and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw all outstanding rejections.

Claim Status

Claims 11-12, 14-15, 17-19, 59, 63-67, and 78-79 are pending in the application, with claims 11, 12, and 18 being the independent claims. Claims 1-10, 13, 16, 20-58, 60-62, 68-77 and 80-85 have been cancelled.

Rejection Under 35 U.S.C. § 102(e)

Claim 20 was rejected under 35 U.S.C. § 102(e) as being anticipated by Horn *et al.* (U.S. Patent No. 6,465,175). By way of the amendment filed September 5, 2006, under 37 CFR § 41.33(b), claim 20 has been cancelled. Thus, the rejection of this claim is rendered moot.

Rejection Under 35 U.S.C. § 103(a)

Claims 11-12, 14-15, 17-20, 59 and 63-67 were rejected under 35 U.S.C. § 103(a), as being unpatentable over Horn *et al.* (US Patent No. 6, 465,175) in view of Tyagi *et al.* (US Patent No. 6,037,130). By way of the amendment filed September 5, 2006, under 37 CFR § 41.33(b), claim 20 has been cancelled and rejection of this claim is rendered moot. Applicants respectfully traverse this rejection with regard to remaining claims 11-12, 14-15, 17-19, 59 and 63-67.

Establishing *prima facie* obviousness requires a showing that some combination of objective teachings in the prior art and/or knowledge available to one of skill in the art would have lead that

individual to arrive at the claimed invention. *See* In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). Proper consideration of the prior art requires that the PTO not pick and choose to apply only those portions of the prior art which support the proposition that the applicants' claimed invention is unpatentable. *Id.* at 1075. This is impermissible hindsight. The Supreme Court has recently warned "of the distortion caused by hindsight bias" and cautioned against "arguments reliant upon ex post reasoning." KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727, 1742 (2007).

It is particularly important that the teachings of prior art references must be considered in their entirety, *i.e.* as a whole, including those parts that teach away from the claimed invention. *See* W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Indeed, the Supreme Court has recently indicated that teaching away from a claimed invention is a likely indicator that the invention is not obvious: "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007). Thus, an "applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997).

The currently pending claims are drawn to methods involving the detection of single-labeled oligonucleotides that are incorporated into synthesized nucleic acids. In particular, the invention defined by independent claim 11 relates to a method for quantifying or detecting nucleic acid molecules during nucleic acid synthesis. The method of claim 11 involves mixing a target nucleic acid with a fluorescently-labeled oligonucleotide. The oligonucleotide has a single type of fluorescent label with the same chemical structure, and undergoes a detectable change in

fluorescence upon hybridization to the target nucleic acid. The mixture containing the target nucleic acid and the fluorescently-labeled oligonucleotide is incubated under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of the target nucleic acid whereby the labeled oligonucleotide is incorporated into the synthesized nucleic acid.

Independent claim 12 relates to a method for quantitation or detection of nucleic acid molecules during nucleic acid amplification. The method of claim 12 involves mixing a target nucleic acid with a fluorescently-labeled oligonucleotide. The oligonucleotide has a single type of fluorescent label with the same chemical structure, and undergoes a detectable change in fluorescence upon hybridization to the target nucleic acid. The mixture containing the target nucleic acid and the fluorescently-labeled oligonucleotide is incubated under conditions sufficient to amplify a nucleic acid molecule complementary to all or a portion of the target nucleic acid whereby the labeled oligonucleotide is incorporated into the amplified nucleic acid.

Independent claim 18 relates to a method for amplifying a double stranded nucleic acid. The method of claim 18 involves the use of primers that have a single type of fluorescent label with the same chemical structure and undergo a detectable change in fluorescence upon hybridization to a complementary nucleic acid. The primers are hybridized to opposite strands of the double stranded target nucleic acid in the presence of a polymerase under conditions sufficient to extend and incorporate the primers into a newly synthesized complementary nucleic acid. Amplification of the double stranded target nucleic acid occurs with repeated rounds of denaturation, hybridization and primer extension.

The Horn reference discloses a probe-based method for detecting target nucleic acids. Horn's method involves mixing target nucleic acid molecules with an oligonucleotide probe having

a single fluorescent label (*i.e.,* a single-labeled probe). The premise behind Horn's detection method is that when a single-labeled probe is in non-hybridized form it provides a detectable fluorescent signal, but when the probe hybridizes to a complementary target nucleic acid it undergoes a spontaneous conformational change and does not fluoresce. *See* Horn column 3, lines 6-20 and column 17, lines 65-67.

The Horn reference does not disclose the use of ***single-labeled primers*** that are ***incorporated into*** synthesized nucleic acids. Detection using the probe-based methods described by Horn is accomplished by nucleic acid hybridization, which does not involve extension and incorporation of a primer in an amplification product to be detected, as is presently claimed. Thus, as the Examiner acknowledges (see Office Action dated January 4, 2006, page 6), Horn fails to teach incorporation of a labeled oligonucleotide into a synthesized nucleic acid product.

The Examiner relies on the Tyagi reference to cure this deficiency. Specifically, the Examiner states that it would have been *prima facie* obvious to "utilize the single label method of Horn with the hairpin primers of Tyagi." *See* Office Action dated January 4, 2006 at page 6. The Examiner states that an ordinary practitioner would "substitute the single label quenching beacons of Horn in the method of Tyagi so that a separate quenching dye is not necessary." *Id.*

The Tyagi reference discloses a molecular beacon-based method for detecting target nucleic acids. Specifically, Tyagi's molecular beacon-based detection method involves mixing target nucleic acids with a multiple-labeled primer or probe having a pair of fluorophores (*i.e.,* a harvester and an emitter moiety) positioned near one end of the primer/probe. The multiple-labeled primers or probes used in Tyagi's molecular beacon-based method also include a fluorescence-quenching moiety, which itself may be a fluorophore and is located at an end of the primer/probe opposite the

emitter and harvester. *See* Tyagi column 2, lines 45-65 and column 5, lines 36-38. The premise behind Tyagi's molecular beacon-based detection method is that upon hybridization to a target nucleic acid the multiple-labeled primer or probe undergoes a conformation change that eliminates quenching and allows detection of fluorescence by the emitter and/or harvester. More specifically, the pair or fluorophores on the primer or probe are allowed to interact by fluorescence resonance energy transfer (FRET) when the quencher label is separated from them by hybridization to a target nucleic acid. *See* Tyagi, column 8, lines 13-60. Tyagi states that the molecular beacon-based detection method "require[s] that the two fluorophores be separated by an appropriate distance and that the emission spectrum of the harvester moiety significantly overlaps the absorption spectrum of the emitter moiety." *See* column 7, lines 46-50 (emphasis added). Because Tyagi teaches the use and requirement of ***multiple***-labeled rather than ***single***-labeled oligonucleotides – and therefore teaches away from the presently claimed invention – Tyagi cannot properly be relied upon to cure the deficiency of the Horn reference.

Even if the Tyagi reference were properly relied upon to cure the deficiency of the Horn reference (which, for the reason set forth above, it cannot), the combination of the cited references fails to yield the claimed invention. Specifically, if Tyagi's molecular beacon primers were modified as the Examiner suggests, (*i.e.,* "so that a separate quenching dye is not necessary"), the skilled artisan simply does not arrive at the claimed invention. This is because Tyagi's invention is based on a primer/probe design that involves multiple labels (*i.e.,* at least three labels: (a) two fluorophores, the emitter and the harvester; and (b) a quencher moeity). Thus, even if a skilled artisan were to remove the quencher from Tyagi's molecular beacon primer as suggested by the Office Action dated January 4, 2006 (page 6), the resultant modified primer would still have ***two***

fluorophores (*i.e.,* an emitter and a harvester), and not just one label as required by the present claims.

For at least the reasons discussed above, *prima facie* obviousness has not been established. First, the Tyagi reference expressly teaches away from the claimed invention and is improperly relied upon to cure the deficiency of the Horn reference. Second, combining the Horn and Tyagi references does not yield the claimed invention. Applicants therefore request that the rejection of claims 11-12, 14-15, 17-19, 59 and 63-67 be withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore request that the Examiner reconsider and withdraw all presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Final Office Action dated January 4, 2006 and, as such, the present application is in condition for allowance.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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